REMARKS

Claims 34, 46-64, 70 and 71 are pending in the application. Claims 46, 53, 56, 57 and 70 have been amended. Support for these amendments can be found in the original claims as filed. Support for new claim 71 can be found in the specification at, *e.g.*, page 6, lines 30-37; Figure 1; and original claims 34 and 35. No new matter has been added.

Specification

The Examiner has objected to the amendment to the specification filed August 3, 2000, the amendment to the figures filed February 8, 2002, and the amendment to the sequence listing filed January 26, 2004 under 35 U.S.C. § 132 as introducing new matter. The Examiner has considered the Declaration of Dr. Franco diGiovine filed March 2, 2001, and admits that "[t]here is no doubt that Applicant has discovered that there is a polymorphism at position +6912 of the IL-1B gene." (See, Office action, page 5.) However, the Examiner asserts that Applicants have not provided sufficient evidence to show possession of the entire sequence of amended SEQ ID NO:2, which is 9271 bases in length, at the time of filing. Id. The Examiner also states that "[s]ince polymorphisms can occur throughout a molecule, one cannot assume that there are no other polymorphisms linked to position +6912 within the 9721 bases of the IL-1B gene, and that the sequence of the rest of the 9721 nucleotides is identical to that reported in the prior art." (See, Office action, paragraph bridging pages 5 and 6.) Applicants traverse.

Applicants assert that Applicants have provided sufficient evidence to show possession of the entire 9271 nucleotides of the amended SEQ ID NO:2 sequence, at the time of filing. In support of this assertion, Applicants file herewith a further Declaration of Dr. diGiovine ("diGiovine Declaration II"), in which Dr. diGiovine provides additional detail regarding the identification and characterization of the claimed nucleic acids. Applicants also file herewith Appendix A, a copy of the laboratory notebook ("the Notebook") containing experiments performed in Dr. diGiovine's laboratory from August 24, 1995 to March 22, 1996.

Dr. diGiovine notes that a PCR product corresponding to the 3'UTR of the IL-1B gene was amplified from human genomic DNA and sequenced, as was described in the instant application (Example 1, pp. 36-37). diGiovine Declaration, ¶ 6. This PCR product was generated using primers that bind to regions of the IL-1B gene corresponding to positions +6720

to +6742 and +7102 to +7123, when the IL-1B gene is numbered in accordance with the numbering of Figure 1. Id. Dr. diGiovine states that the determination that a G to C change at the +6912 location was performed by sequencing of the fragment amplified by the F_2 and B_1 PCR primers, the result of which was recorded on February 21, 1996 on page 116 of the Notebook, using a sequence-specific oligonucleotide primer hybridizing to nucleotides +6913 to +6947 of the IL-1B gene as described on page 118 of the Notebook. Id. The location of the G to C change is further evidenced on page 124 of the Notebook, which is entitled "Further plans for the +8845 polymorphism." Dr. diGiovine explains that position +6912 in Figure 1 corresponds to nucleotide 8845 of SEQ ID NO: 1, and that the allele containing this polymorphism is also referred to as "IL-1B (+6912) allele 2." diGiovine Declaration, ¶ 4. Thus, Applicants have provided substantial evidence to show possession of the IL-1B (+6912) allele 2 polymorphism at the time the present application was filed.

Dr. diGiovine also addresses the Examiner's statement that "[s]ince polymorphisms can occur throughout a molecule, one cannot assume that there are no other polymorphisms linked to position +6912 within the 9721 bases of the IL-1B gene, and that the sequence of the rest of the 9721 nucleotides is identical to that reported in the prior art." (See, Office action at pages 5-6). Dr. diGiovine explains that the C polymorphism at position +6912 is a single nucleotide polymorphism, or "SNP." diGiovine Declaration, ¶ 8. A SNP is known in the art as a DNA sequence variation among individuals in which the purine or pyrimidine base (as guanine) of a single nucleotide in the genome has been replaced by another such base (as cytosine). Id. Dr. diGiovine concludes that one of skill in the art would recognize that the sequence of the rest of the 9721 nucleotides of IL-1B is identical to the wild-type sequence, which has been reported in the art, and that upon identifying the SNP at position +6912, it was unnecessary to re-sequence the entire IL-1B gene. Id.

In regard to the Examiner's statement regarding linkage analysis of the IL-1B +6912 with other IL-1B polymorphisms, Dr. diGiovine opines that genetic linkage between alleles of a given gene such as IL-1B does not indicate the presence of multiple sequence variations in the IL-1B gene of an individual. diGiovine Declaration, ¶ 8. Instead, linkage analysis is useful to demonstrate co-segregating polymorphisms that contribute to a given disease or disorder. Id. Indeed, linkage analysis was performed under Dr. diGiovine's direction on or about February 23,

1996 between the IL-1B (+6912) locus and the IL-1B *taq* locus, and the result is shown on page 129 of the Notebook. Id. The data generated by these analyses demonstrate that the IL-1B (+6912) allele 1 (termed "Allele (G)" in the notebook) is 100% associated with the IL-1B *taq* allele 2, while the IL-1B (+6912) allele 2 (termed "Allele (C)" in the notebook) is 100% associated with the IL-1B *taq* allele 1. Id.

The data contained in the linkage experiments recorded on page 129 of the Notebook also rebut the Examiner's contention that the changes to the specification which reverse the designations of "allele 1" and "allele 2" appear to represent new matter. (See, Office action, page 6). In fact, it is clear the Applicants regarded the IL-1B (+6912) allele 1 to have a guanine at position +6912, while the IL-1B (+6912) allele 2 was known to have a cytosine at position +6912 of the IL-1B gene.

Moreover, Dr. diGiovine explains that the human IL-1B gene sequence published by Clark *et al.* (Nucleic Acids Research 14(20):7897-7914 (1986)) and deposited in GenBank under the accession number X04500 was regarded as the standard sequence for human IL-1B. diGiovine Declaration, ¶ 10. Dr. diGiovine notes that the Clark *et al.* sequence shows a "G" at position +6912. Id. The "G" variation was named "allele 1" and the "C" variation, the allele discovered by Applicants that contains a "C" at position +6912, was named "allele 2." Id. Thus, the statement in the application indicating that the IL-1B allele 1 has a cytosine at position +6912 and that allele 2 has a guanine at that position is a typographical error. Id. Further, measurements of allele frequency presented in the patent application (*e.g.,* Example 2, pp. 37-38) demonstrate that allele 1 is the more frequent allele, and Dr. diGiovine concludes that this allele should be considered the wild-type allele. Finally, Dr. diGiovine also cites numerous publications and database entries that have presented the Clark *et al.* nucleic acid sequence as the wild-type sequence. (See, *e.g.,* US Patent numbers 5,686,246; 6,720,141; 6,730,476; and 6,746,839; and GenBank Accession number P01584). diGiovine Declaration, ¶ 10.

For the above-stated reasons, Applicants assert that sufficient evidence shows that at the time of filing, Applicants were in possession of the entire 9271 nucleotides of the amended SEQ ID NO:2 sequence. Thus, this objection to the specification should be withdrawn.

Claim Objections

Claims 54-57 have been objected to under 37 CFR 1.75(c) as being in improper dependent form for failing to further limit the subject matter of a previous claims. Applicants have amended claims 54, 56 and 57 to be in independent form. Claim 55 depends from and limits the subject matter of claim 54.

Claim 70 is objected to because the word "nucleic" was misspelled and the use of the word "vector is unclear." Applicants have amended claim 70 to correct the typographical error and to replace the word "comprises" following the word "vector" with the word "is", as suggested by the Examiner.

Therefore, these objections have been overcome and should be withdrawn.

Claim Rejections

35 U.S.C. § 112, first paragraph

Claims 34, 46-64 and 70 have been rejected under 35 U.S.C. § 112, first paragraph for lack of written description. According to the Examiner, one of skill in the art could not have come to the conclusion that Applicant was in possession of SEQ ID NO: 2 (as amended) at the time the invention was filed. (See Office action, page 10). For the reasons stated above, Applicants assert that Applicants have provided sufficient evidence to show possession of the entire 9271 nucleotides of the amended SEQ ID NO:2 sequence, at the time of filing. Therefore, one of skill in the art would recognize that Applicant was in possession of the claimed invention at the time the application was filed. This rejection should be withdrawn.

35 U.S.C. § 102

Claim 53 has been rejected as being anticipated by Brennan, US Patent 5,474,796 ("Brennan"). As suggested by the Examiner, Applicants have amended claim 53 herein to specify that the claimed nucleic acid is a "complement to the entire length of the isolated nucleic acid of claim 46." As Brennan does not teach the entire length of the isolated nucleic acid of claim 46, this reference does not contain all the limitations of claim 53. Therefore, Brennan does not anticipate amended claim 53, and this rejection should be withdrawn.

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance, and a Notice of Allowance is respectfully requested. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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